UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/741,534	12/19/2003	Alain Baron	18528.675 / 0218-UTL-9	5134

28381 7590 02/12/2007

ARNOLD & PORTER LLP
ATTN: IP DOCKETING DEPT.
555 TWELFTH STREET, N.W.
WASHINGTON, DC 20004-1206

EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/741,534	BARON ET AL.	
	Examiner	Art Unit	
	Elly-Gerald Stoica	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *3,12,21,30 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-11,13-20,22-29, 31-38 and 40-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :07/01/2004, 11/15/2004, 01/21/2005.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of the species GLP-I (7-36) (SEQ ID NO: 1) in the reply filed on 11/09/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the claims

2. The claims 1-46 are pending. Claims 3, 12, 21, 30, and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/09/2006. The claims 1, 2, 4-11, 13-20, 22-29, 31-38 and 40-46 are currently examined.

Specification

3. Claim 28 is objected to because of the following informalities: the word "reduce" in the claim should read "reducing". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Specifically, the specification discloses that "an analog" includes any polypeptide and which has at least about 50% sequence identity with an amino acid sequence encoding a base molecule whether or not including insertions, substitutions, extensions, or deletions. Such analogs may comprise conservative or non-conservative amino acid substitutions (including non-natural amino acids. An "agonist analog," is an analog that exhibits at least one characteristic or action of the base molecule, preferably having potency better than the base molecule, or **within five orders of magnitude (plus or minus) of potency compared to the base molecule**. A "derivative" includes any base molecule or analog having a chemical

modification within, attached, linked to, or associated with the molecule. Such chemical modifications can include internal linkers (e.g., spacing or structure-inducing) or appended molecules, such as molecular weight-enhancing molecules (e.g., polyethylene glycol (PEG), polyamino acid moieties, etc.), or tissue targeting molecules. Finally, a "variant" includes any modification to the base molecule not encompassed in the terms "analog" and "derivative" (p4-5). However, the specification does not teach any functional variant, fragment, or derivative of the GLP-1 other than the full-length sequence of SEQ ID NO: 1.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue

experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

5. Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to administering a composition containing a compound which is which is an incretin, a GLP-1, an exendin, binds to a receptor for GLP-1 or a biologically active agonist, analog, derivative, variant, or fragment of any of them. On pages 4-5 it is recited that "an analog" includes any polypeptide and which has at least about 50% sequence identity with an amino acid sequence encoding a base molecule whether or not including insertions, substitutions, extensions, or deletions. Such analogs may comprise conservative or non-conservative amino acid substitutions (including non-natural amino acids. An "agonist analog," is an analog that exhibits at least one characteristic or action of the base molecule, preferably having a potency better than the base molecule, or **within five orders of magnitude (plus or minus) of potency compared to the base molecule**. A "derivative" includes any base molecule or analog having a chemical modification within, attached, linked to, or associated with the molecule. Such chemical modifications can include internal linkers (e.g., spacing or structure-inducing) or appended molecules, such as molecular weight-enhancing molecules (e.g., polyethylene glycol (PEG), polyamino acid moieties, etc.), or tissue targeting molecules. Finally, a "variant" includes any modification to the base molecule not encompassed in the terms "analog" and "derivative". The claims do not

require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The biological functionality of binding to a receptor for GLP-1 is offered as a member of a Markush group. Thus, the claims are drawn to a genus of polypeptides that are undefined.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one amino acid species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments and with at least 50% sequence identity to a amino acid comprising the sequence of SEQ ID NO: 1 (the base molecule).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the polypeptide of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For claims 1-46 it is not clear what are the metes and bounds of the claims since anything (since any variant derivative, or variant or mutation of a base molecule or a peptide having 50% identity) could be used, according to the claims to perform the invention.

With regard to claims 1-9, it is not clear how can one prevent a nephropathy in a subject having nephropathy.

With regard to claims 10-18, it is not clear **what** has to be prevented from progression to ESRD, as it is also not clear what ESRD means, since it is not spelled-out in the claim.

With regard to claims 19-27 it is not clear what the meaning of the improvement of the endothelial function is and as such the metes and bounds of the claims cannot be established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 4-11,13-20, 22-29, 31-38 and 40-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Coolidge et al. (WO 01/89554, 11/29/2001).

The claims are drawn to a method for preventing or treating a subject having nephropathy (claims 1 and 2) or for preventing progression to ESRD (claims 10-11), or of improving endothelial function in a subject in need thereof (claims 19 and 20), or of reducing proteinuria in a patient (claims 28 and 29), or for preventing or slowing progression of glomerulosclerosis (claims 37 and 38), comprising: administering to an individual in need of such treatment an effective amount of a compound which is a GLP-1 or a biologically active agonist, analog, derivative, variant, or fragment of it. Each of the main claims is further limited by dosage, rate of administration and mode of administration as follows:

- from about 0.001 pmol/kg to about 20nmol/kg (claims 4, 22, 31, and 40).
- from about 0.001 µg/kg/dose to about 1.0 µg/kg/dose (claims 5, 23, 32, and 41).
- the dose should achieve a plasma level of at least 40pg/ml (claims 6, 24, 33, and 42).
- the administration is parenterally (claims 7, 25, 34 and 43).
- the intravenous dose is from about 0.1 pmol/kg/min. up to about 10 pmol/kg/min (claims 8, 26, 35, and 44)
- the subcutaneous dose is from about 0.1 pmol/kg/min to 75 pmol/kg/min (claims 9, 27, 36, and 45).

Coolidge et al. teach a method of treatment, using GLP-1, of an individual with cardiac abnormalities consistent with ischemic heart disease (p28, lines 5-18). The

continuous administration doses taught are 0.1-10 pmol/kg/min, or from 0.5-50 pmol/kg/min, for subcutaneous administration (p 19, lines 22-26), which are well within the limits of the claims of the instant application. The parenteral administration route of the instant claims could be any of the intravenous or subcutaneous routes of Coolidge at al. The biological properties of the GLP-1 are intrinsically related to its structure and its function is inherent. Therefore the GLP-1 molecule of the invention of Coolidge et al. would bind and exert its action irrespective of the condition sought to be treated. No meaningful weight can be given to the limitations of the claims that recite specific doses because there is no specific agent being administered and, moreover, the specification admits at pages 4-5 that activity can vary within 5 orders of magnitude.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coolidge et al. (WO 01/89554, 11/29/2001), in view of Guitard et al. (US 2001/0016586, 08/23/2001). The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1,

148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

- The claims are drawn to a method for preventing or treating a subject having nephropathy wherein the nephropathy is caused by diabetes, insulin resistance, or hypertension (claim 46

The teachings of Coolidge et al. and their interpretation were presented supra. Coolidge et al. does not mention that the conditions are caused by diabetes, insulin resistance, or hypertension. Guitard et al. teach the use of GLP-1, as a hypoglycemic agent, in nephropathies, peripheral angiopathies, hypertension, microangiopathic changes, diabetes and insulin resistance. It would have been obvious to one of skill in the art to modify the methods taught by Coolidge et al. in the diseases taught by Guitard et al., with a reasonable expectation of success. Motivation to do so comes from the common etiology of the nephropathies, which are linked to insulin metabolism deregulation that may be controlled by GLP-1, as taught by Coolidge et al.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elly-Gerald Stoica whose telephone number is (571) 272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER